Identifying growth velocity discontinuities in the first postnatal year brain development with diffusion tensor imaging

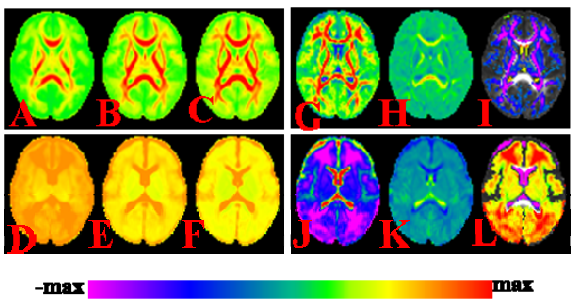
Y. Chen[1], H. Zhu[2], J. Wang[2], H. An[1], D. Shen[1], and W. Lin[1]

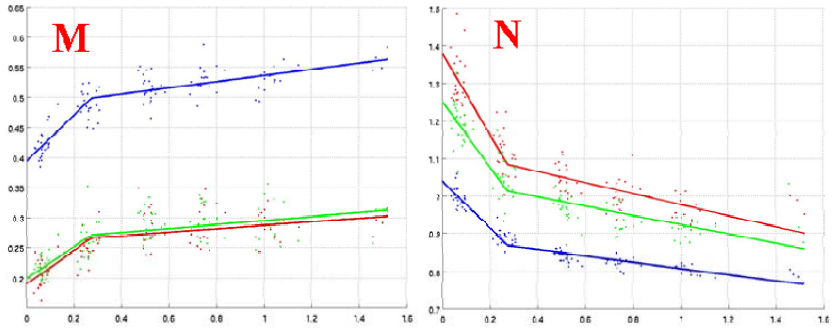
[1]Radiology, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC, United States, [2]Biostatistics, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC, United States

Introduction: Substantial insights towards early brain development have been gained with diffusion tensor imaging (DTI) through quantitative comparisons between the diffusion indices such as fractional anisotropy (FA) and mean diffusivity (MD) across different age groups. Even though it has been revealed that early brain development is a nonlinear process, detailed understanding of the normal brain growth within the first postnatal year remains lacking. To the best of our knowledge, there are only two DTI based previous studies focusing on this age span [1, 2]. The study by Dubios *et al* leaned towards the feasibility of tractography in early postnatal population [1]. The study by Provenzale *et al* may be the only growth trajectory related study within the first postnatal year [2]. Based upon a few ROIs, this study qualitatively found that brain maturations can be roughly broken into two linear segments in these ROIs including a fast initial and a slower maturation separated at 100 days (~0.274 years). In our study, we will employ a voxel based analysis on commonly used DTI parameters including FA and MD to examine whether the growth velocities are discontinuous at 100 days within the first postnatal year.

Methods: This study was approved by institutional review board. Written consents were obtained from parents before image acquisition. Thirty five (15M and 20F) full-term healthy infants were recruited for this longitudinal study leading to 105 datasets (ages at scan 184.86±138.43 days, min 13 days and max 555 days) so far. DTI with 42 encoding directions were acquired after the subjects were spontaneously sleeping inside the scanner wearing proper ear protections. No sedative drugs were used during the imaging session. DTI parameters including FA, MD and the three principal diffusivities were computed with FSL. FA images were registered towards a template FA image (not included in the sequential regression analysis) with an elastic registration technique utilizing the neighborhood derived image features [3]. The regression analysis was performed with generalized estimating equations, which is a well established longitudinal statistical method and able to handle the missing data situation and repeated measurements from the same subjects [4]. The temporal growth pattern of one DTI parameter in consideration with discontinuity was modeled as $E(y_{i,j}) = u_{i,j} = \beta_0 + \beta_1 * t_{i,j} + \beta_2 * \lfloor t_{i,j} - 0.274 \rfloor$, where, $\lfloor t_{i,j} - 0.274 \rfloor = t_{i,j} - 0.274$ if $t_{i,j} \geq 0.274$ and $\lfloor t_{i,j} - 0.274 \rfloor = 0$, if $t_{i,j} < 0.274$. Equivalently, the growth velocities of one DTI parameter was β_1 and $\beta_1 + \beta_2$ respectively before and after the break point (0.274 years). Through testing the null hypothesis $\beta_2 = 0$, we are able to reveal the brain regions with significant change in growth velocity as the regions rejecting this null hypothesis. Multiple comparisons were corrected through controlling the false discovery rate to less than 5%.

Results: One slice of the estimated FA and MD images at birth, at the break point and year 1 were given in (**A**,**B**,**C**) and (**D**,**E**,**F**) respectively for FA and MD. The growth velocity maps from the same slice location before (β_1) and after ($\beta_1 + \beta_2$) the break point were given in (**G**,**H**) and (**J**,**K**) respectively for FA and MD. **I** and **L** demonstrated significant changes in growth velocity after the break point (β_2 map) for FA and MD, the color encoded regions in **I** and **L** were the brain regions where the previously mentioned null hypothesis were rejected (after adjustment for multiple comparisons). In **I**, most brain regions showed negative values in β_2, demonstrating the after the break point, the growth velocity became smaller for FA as apparent in the lower values in **H** compared to **G**. In MD, most brain regions demonstrated positive β_2, demonstrating the reduction velocity in MD becomes less steeper after the break point (as apparent in **J** and **K**). In both FA and MD, corpus callosum (especially splenium) did not demonstrate significant change in growth velocity before and after the break point. We further demonstrated the estimated growth trajectories with the scattered data points to be fitted in three brain regions including superior frontal (red curve in **M** and **N**), superior parietal white matter (green curve in **M** and **N**) and posterior limbs of internal capsule (blue curve in **M** and **N**). We picked these regions to cover both the peripheral and deep white matters. It is worth pointing out that with visual inspection, the scattered data plots also supported the detected discontinuities in growth velocities at 100 days in these brain regions. These results also agreed with previous findings that central brain regions have a high FA and lower MD values compared to peripheral brain areas.





Discussion:

We have demonstrated that our longitudinal regression analysis is able to reveal the existence of wide-spread discontinuities in growth velocities within brain in FA and MD. To the best of our knowledge, this study may be the first systematic and quantitative longitudinal analysis of growth trajectories of DTI within the first postnatal life. More importantly, our findings agree with one major postmortem study concerning the myelin basic protein expression in parietal white matter, which revealed two periods with rapid myelin change as 43~54 and 72~92 postconceptual weeks [5]. The break point at 100 days within white matter may correspond to the ending of the first rapid phase in myelination (54 postconceptual weeks correspond to 14 postnatal weeks). Furthermore, our voxel based results may support the existence of this break point in most brain regions excluding corpus callosum, which may be caused by the complexity associated with the axonal reduction in this area or corpus callosum may have a break point different from 100 days. Thus, one immediate extension to this work is to examine whether different brain regions having different break points. In conclusion, we have demonstrated that it is very promising to establish the connection between the growth trajectories of DTI parameters with early postnatal white matter myelination.

Referene: [1] Dubios, et al Neuroimage 2006:30,1121-32. [2] Provenzale, et al. AJR,2007 189:476-86. [3] Shen et al, IEEE-TMI, 21(11), 1421-39, 2002. [4] Liang, et al. Biometrika, 1986:73, 13-22. [5] Haynes, et al. J Comp Neurol 2005, 484: 156-67.